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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,128	07/28/2005	Piotr Graczyk	102286.154US1	4053

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WILMERHALE/BOSTON
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EXAMINER
LOEWE, SUN JAE Y

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
01/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/509,128	GRACZYK ET AL.	
	Examiner	Art Unit	
	Sun Jae Y. Loewe	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40,48,49,58-60 and 62-66* is/are pending in the application.

4a) Of the above claim(s) *17-27,31,33-40,48,49,58-60,62 and 63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,28-30,32 and 64-66* is/are rejected.

7)☒ Claim(s) *16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-10-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-40, 48, 49, 58-60 and 62-66 are pending in the instant application. Claims 41-47, 50-57 and 61 were cancelled by preliminary amendment filed on July 28, 2005.

Election/Restrictions

2. The election of species requirement set forth on September 12, 2007 is withdrawn.

3. Applicant's election with traverse of Group I in the reply filed on November 13, 2007 is acknowledged. The traversal is on the ground(s):

> " Further, Applicants respectfully disagree with the Examiner's conclusion that the claims of the present application are directed to more than one species of the generic invention, as they are held to relate to compounds encompassed by the generic definition of Formula (I), obtained "

It is maintained that the claims do encompass multiple species of Formula (I)

> " The core structure linking the subject matter of groups I-IX is therefore a 7-azaindole substituted at both the 3- and the 5-position. Such a core structure is not disclosed in the Kruber document and the claims therefore do not lack unity. "

The substituents at the 3- and 5-position of the azaindole core are variables and thus do not constitute a structural feature shared by the claimed compounds. Thus, it is maintained that the core structure is that shown on p. 3 of the restriction requirement dated September 12, 2007.

The arguments are not found persuasive for the reasons provided above. The restriction requirement is still deemed proper and is therefore made FINAL.

4. Claims 17-27, 31, 33-40, 48, 49, 58-60, 62 and 63 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter. Applicant timely traversed the restriction (election) requirement in the reply filed on November 13, 2007.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on May 10, 2006 was filed in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS was considered. A signed copy of form 1449 is enclosed herewith.

Claim Objections

7. Claims 1-15, 28-30, 32 and 64-66 objected to for containing non-elected subject matter.

8. Claim 16 objected to for being dependent on a base rejected claim.

9. Claim 4 objected to because of the following informality: the definition of R is neither in proper Markush nor proper alternative form.

10. Claim 12 objected to because of the following informality. The claim is drawn to "straight of branched chain C_{1-4}". The following wording (or similar) is suggested: "straight or branched chain C_{1-4} alkyl."

11. Claim 32 is objected to because of the following informality: the claims refer to the terms "for us." It appears that this is a typographical error and should read "for use."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-15, 28-30, 32 and 64-66 rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.
>
> Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:
>
> > "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

I. ***<u>Scope of Claims</u>***

Compounds of Formula (I) wherein "Z=oxygen, X=NR^5, R=phenyl or naphthyl,"

The following variables are claimed broader than what is supported by the disclosure:

Optional Substituent to R:	for claims 1-5, 7-15, 28-30 and 32
R":	for claims 1, 3-15, 28-30, 32 and 64-66
R^5:	for all claims
Y:	for claims 1-7, 9-11, 13-15, 28-30, 32 and 64-66

R': for claims 1-6, 9-15, 28-30, 32 and 64-66

II. Scope of Disclosure

Reduction to Practice:

The compounds reduced to practice support the following definitions for the variables noted.

Optional Substituent to R:	halogen, NR^2R^2 wherein R^2=H or unsubstituted alkyl
R':	H or unsubstituted C_{1-6} alkyl
R^5:	H or unsubstituted C_{1-4} alkyl
Y:	absent, NR^6, CR^6R^6, or C_{1-4} alkylene wherein R^6=H, unsubstituted C_{1-4} alkyl
R':	C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, carbocyclyl optionally substituted with halogen, haloalkyl, C_{1-12} alkyl, OR^2 wherein R^2=H or unsubstituted alkyl

Reduction to Structural or Chemical Formulas:

The only disclosure, in addition to the species reduced to practice, is in form of *lists* of possible groups (eg., imidazolidine, indole, indoline, for heterocycle). This type of disclosure is not a representation of any of the species it entails. A"laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Therefore, there is no disclosure of species (eg. by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function:

A correlation between structure and function, for the instantly claimed genus of

compounds, is neither known in the art nor disclosed in the specification. Thus, it is not understood what *specific structures* for the variables noted will lead to compounds that have the instantly claimed activity.

III. *Analysis of Fulfillment of Written Description Requirement:*

The structure/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC_{50} data of multiple compounds with various types of structural modifications. These types of studies provide insight into the structural limitations that are required for activity, ie. specific structural elements tolerated for the claimed activity. In the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by claims 1-15, 28-30, 32 and 64-66; (ii) disclosure of species supporting genus is limited to compounds reduced to practice, which scope is not commensurate with the scope of genus/subgenus claimed; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

(Enablement)

13. Claims 1-15, 28-30, 32 and 64-66 rejected under 35 U.S.C. 112, first paragraph. The specification is *enabling* for the use of the compounds that have adequate written description (see Section 12). The specification is *not enabling* for the use of compounds not supported by the disclosure.

In conclusion, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue". The factors are applied below to the instant claims.

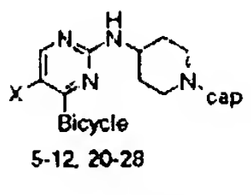
The breadth of the claims
Compounds not supported by the disclosure (see above section 12.I and 12.II.).

The nature of the invention
The compounds are disclosed to be inhibitors of C-Jun N terminal kinases (eg. JNK3). An alternate utility is neither disclosed in the specification nor known in the art for this genus of compounds.

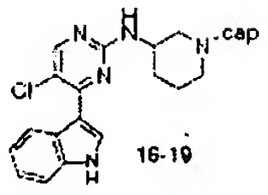
The state of the prior art/level of ordinary skill/level of predictability
The level of ordinary skill is high, but the level of predictability in the art is low. Although SAR studies are not available for the instantly claimed genus of compounds, these studies have been disclosed for other compounds with the same utility, see example below.

- Alam et al. (Bioorg. Med. Chem. Lett., 17, 2007, 3463-3467), Table 1:

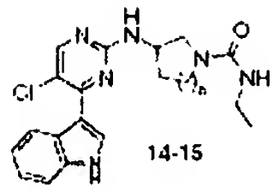
Table 1. Enzymatic and cellular activity of aminopyrimidine analogues



Bicycle
5-12, 20-28



16-19



14-15

Compound	5' X	Bicycle	Heterocycle	Cap	JNK1[41] IC_{50} (nM)	JNK2[41] IC_{50} (nM)	JNK3[41] IC_{50} (nM)	CDK2[42] IC_{50} (nM)	c-Jun[43] IC_{50} (nM)
5	CN	6-F-3-Indole	4-Piperidine	CONHEt	92	67	412	412	3700
6	Cl	3-Indole	4-Piperidine	CONHEt	13	25	57	1517	704
7	Me	3-Indole	4-Piperidine	CONHEt	320	250	410	IA	10,000
8	H	3-Indole	4-Piperidine	CONHEt	74	245	na	10,000	8091
9	Cl	3-Imidazopyridine	4-Piperidine	CONHEt	41	55	na	605	7723
10	Cl	1-Indole	4-Piperidine	CONHEt	457	709	na	4443	>10,000
11	H	3-Imidazopyridine	4-Piperidine	CONHEt	59	281	709	4219	19,331
12	H	1-Indole	4-Piperidine	CONHEt	71	512	na	10,000	29,891
13	H	Pyrazolopyridine	4-Piperidine	CONHEt	69	194	na	8663	4000
14	Cl	3-Indole	3-Pyrrolidine	CONHEt	360	177	582	2483	6268
15	Cl	3-Indole	Azetidine	CONHEt	1340	1551	5000	na	4272
16	Cl	3-Indole	3-(*S*)-Piperidine	CONHEt	29	15	32	555	6995
17	Cl	3-Indole	3-(*S*)-Piperidine	$CH_2CONHMe$	139	267	na	>10,000	14,667
18	Cl	3-Indole	3-(*R*)-Piperidine	CONHEt	60	88	107	1264	3583
19	Cl	3-Indole	3-(*R*)-Piperidine	$CH_2CONHMe$	15	31	31	612	2807
20	Cl	3-Indole	4-Piperidine	$CH_2CONHMe$	13	22	14	123	1769
21	Cl	3-Indole	4-Piperidine	COOEt	37	49	82	na	na
22	Cl	3-Indole	4-Piperidine	$CONMe_2$	15	37	na	4358	741
23	Cl	3-Indole	4-Piperidine	CO(4-Me piperazine)	18	26	na	5281	2770
24	Cl	3-Indole	4-Piperidine	$COCH_2NHCOMe$	28	46	na	551	1938
25	Cl	3-Indole	4-Piperidine	$COCH_2NHMe$	67	85	179	2672	2028
26	Cl	3-Indole	4-Piperidine	$COCH_2NMe_2$	57	45	120	1126	3497
27	Cl	3-Indole	4-Piperidine	CO(4-Me piperidine)	15	14	48	1895	813
28	Cl	3-Indole	4-Piperidine	CONH(4-Me piperidine)	47	62	na	6652	807

na, not available.

As discussed in section 12, it is not known what structural limitations are required for preservation of activity within the genus. In view of the low level of predictability one of ordinary skill would not know what structural modifications within the unrepresented genus (ie. unrepresented by the disclosure), if any, would lead to compounds that are active.

The amount of direction provided by the inventor/existence of working examples
Direction and working examples are limited to the genus of compounds that have adequate written description support (see Section 12.II).

The quantity of experimentation needed to make or use the invention

It is not known which of the unrepresented compounds meet the structural requirements for activity. Thus, one of ordinary skill would not be enabled by the disclosure to make/use the claimed C-Jun Kinase inhibitors. The amount of experimentation needed to practice the invention is undue. Further, absent an alternate utility, one of ordinary skill would not be enabled to use the compounds within the genus that are not adequately supported in the disclosure.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 11 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 11 recites the broad recitation X is

NR5, and the claim also recites X is most preferably NH, which is the narrower statement of the range/limitation.

14. Claim 1 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim refers to "(a) A compound of formula (I)," and "(b) the pharmaceutically acceptable salts...". It is unclear whether Applicant intends to claim a mixture of separate embodiments (eg. compound and salt), or whether the terms are alternatives (eg. compound or salt). If the latter is correct, the following wording (or similar) is suggested: "A compound of formula (I) or a pharmaceutically acceptable salt..." For the purpose of examination, the claims were interpreted to encompass alternative embodiments.

15. Claim 1 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim refers to "(c) biohydrolyzable derivatives thereof." The metes and bounds for this embodiment cannot be ascertained. Thus, the inclusion of this embodiment makes the claim indefinite.

Conclusion

16. No claims allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sun Jae Y. Loewe whose telephone number is (571) 272-9074. The examiner can normally be reached on M-F 7:30-5:00 Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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